SYNOPSIS

TITLE OF PROPOSED RESEARCH WORK

Synthesis and Study of Various biologically important aliphatic and aromatic amino acetyl derivatives of substituted 2 - amino benzothiazole

विभिन्न जैविक महत्वपूर्ण प्रतिस्थापित 2-ऐमीनो बेंजोथायाजोल के ऐलिफैटिक और ऐरोमैटिक ऐमीनो ऐसीटिल व्युत्पन्नों का संश्लेषण एवं अध्ययन

Submitted To

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For Ph.D. in Chemistry

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Introduction

"Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties and applications of these heterocycles".

Heterocyclic compounds are a ring compounds having heteroatoms that are atoms of elements other than carbon. The most common atoms are N, S and O which are present in heterocyclic compounds. N and S containing heterocyles play an important role not only for life sciences but also in many other industrial fields related to special & fine chemistry.

Benzothiazole is a heterocyclic compound, weak base, the bicyclic ring system, consists of thiazole ring fused with benzene ring, having various biological activities. Benzothiazole and its 2 - amino derivatives have biological activities like anthelmintic, antidiabetic, antimicrobial, anti- inflammatory, antiviral and anticancer etc. which are useful in medicinal chemistry with applications in drugs discovery. They have also found applications in industries as antioxidants, accelerators and in vulacanization.

Chloro acetyl chloride is a chlorinated acyl chloride. It is bifunctional compound, making it a useful building block material. The major use of chloro acetyl chloride is as an intermediate which make it important in various biologically active compounds to play an important role.

In continuation of our work on synthesis, evalution and numerous biological activities of 2- amino benzothiazole with other heterocyclic compounds is a well known approach to design new drug like molecules with better medicinal properties.

In the view of biological significance of 2 - amino benzothaizole derivatives, it is yet to be explored synthetically and biologically with several other important heterocyclic systems for achieving new and greater biological activities.

Annexure-I (b)

Importance of proposed investigation

In recent year, heterocyclic compound analogues and derivatives have attracted strong interest and importance due to their useful biological and pharmacological properties.

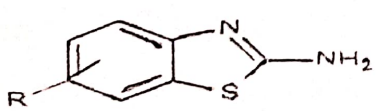
The benzothiazole nucleus and its 2 - amino derivatives [I] possess various diverse biological properties such as anti-inflammatory, anticancer, antiviral, antifungal, antimicrobial, analgesic, antidiabetic, anticonvulsant, anti HIV agents etc. These activities are also possessed by its substituted derivatives as well.

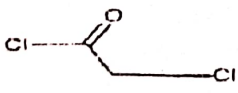
Similarly, chloro acetyl chloride [II] with heterocyclic compounds also possess a wide spectrum of biological activities like antibacterial, pesticidal, antioxidant, plant growth regulator and herbicidal etc.

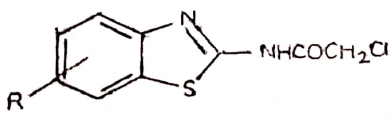
Further, the title compounds, (1'-chloro acetyl) substituted 2 - amino benzothiazole [III] and various aliphatic and aromatic amine derivatives [IV] also exhibit a long range of pharmaceutical properties including antibacterial, anthelmintic, anti-tumor etc.

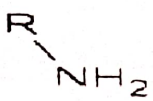
Therefore, the proposed research work is aimed to synthesize a series of some new heterocyclic compounds containing (1'-chloro acetyl) substituted 2 - amino benzothiazole and various amine (aliphatic and aromatic) derivatives in the same compound with better and enhanced biological activities.

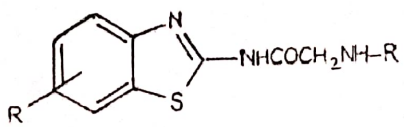
We hope that these individual pharmacological properties of above compounds may impart enhanced biological activities to the resulting compound [V] and these new compounds will be used in medicinal chemistry as therapeutic agents.

(I) 

(II) 

(III) 

(IV) 

(V) 

Annexure-I(c)

Objectives

The main objectives of proposed research work are as follows:-

1. To synthesize substituted 2 - amino benzothiazole by thiocyanogention of substituted aniline.
2. To synthesize chloro acetyl chloride.
3. To synthesize (1'-chloro acetyl) substituted 2 - amino benzothiazole.
4. To synthesize various aliphatic and aromatic amino acetyl derivatives of substituted 2 - amino benzothiazoles.
5. The structure of above synthesized compound will be supported by their elemental analysis and spectral studies (IR, NMR, Mass etc).
6. The new heterocyclic compounds will be examined for their biological activities like antimicrobial, antibacterial, antifungal, anticancer etc.

Annexure-II

Review of work already done on the subject of proposed research work

According to proposed research work, benzothiazole and several of their derivatives have been studied to be of greater interest in view of their varied biological and pharmacological properties [1]. They were found to possess numerous pharmacological activities like anticancer [2-3], antimicrobial [4-5], antimalarial [6], antimycobacterial [7], antiproliferative [8], antioxidant [9-10] and antidiabetic activities [11] etc.

Benzothiazole nucleus containing molecules are also reported as anti HIV agents [12]. Benzothiazole derivatives also possess wide spectrum of chemotherapeutic properties such as antibacterial [13-14], anthelmintic [15], antinociceptive [16], anticonvulsant [17-18], anti-inflammatory [19-20] and antitubercular [21] etc.

Some other benzothiazole derivatives have been found to act as A_{2A} receptor antagonist [22], Schistomicidal agents [23], antirheumatic [24], antiparasitic [25] antiulcer [26], antitumor [27] and antileishmanial [28] and diuretic [29].

The other review focused us that some bioactive derivatives incorporating benzothiazole moity were screened for their entomological [antifeedent activity, acaricidal activity, contact toxicity, stomach toxicity] activities [30], antipsychotic [31], antialzeimer [32], and protein tyrosine inhibitor activities [33].

Based on literature review, a long range of 2 - amino benzothiazole and its substituted 2 - amino benzothiazole derivatives have been reported to possess muscle relaxant [34], cytotoxic [35], antibiofilm agents [36] anticonvulsant [37], anti bacterial [38], anti-inflammatory [39-40], antimicrobial [41-42], analgesic [43-44] and anthelmintic [45], antifungal [46] activities.

Several new substituted 2 - amino benzothiazole derivatives have also shown inhibitive effect on mild steel corrosion [47-48] and plant growth regulatory effect [49].

Heterocyclic molecules having chloro acetyl chloride moiety have also exhibited biological activities like pesticidal [50], antibacterial [51], antifungal [52] and antimicrobial activities [53].

(1`- chloro acetyl) substituted 2 - amino benzothiazole and various aliphatic and aromatic amine derivatives have a significant class of potential drug in medicinal chemistry due to their synthetic flexibility and biological activities such as antioxidants [54], antimicrobial [55-56], antibacterial [57-58], anticancer [59], antidiabetic [60] and antifungal [61].

The literature review reveals that above mentioned compounds have remarkable pharmacological potentialities. This review is mainly an attempt to get the idea for synthesis of some new heterocylic compounds containing two moieties viz. (1`-chloro acetyl) substituted 2 - amino benzothiazole and various aliphatic and aromatic amine derivatives in the same compound with the expectation to achieve some new & improved drugs with their important pharmacological as well as industrial applications.

Annexure-III

Research gap identified in the proposed field of investigation

According to survey of literature, N and S containing heterocyclic compounds is the basic skeleton for number of drug molecules available in the market.

This survey denotes substituted 2 - amino benzothiazole, chloro acetyl chloride and various aliphatic and aromatic amine derivatives exhibit that compounds with these nuclei have vast importance in synthesis as well as pharmaceutical chemistry because of their potent and significant biological activities.

It must be emphasized that combination of substituted 2 - amino benzothiazole with other heterocyclic compounds is a well known approach to design new drug like molecules, which allows achieving new pharmacological profile, action and toxicity lowering.

A number of substituted 2 - amino benzothiazole derivatives have been studied and found to have diverse chemical reactivity and broad spectrum of biological activities like antitumour, anthelmintic, antibacterial etc. Similarly chloro acetyl chloride and various aliphatic and aromatic amine derivatives are also useful as antibacterial, antifungal, antimicrobial and variety of useful drugs.

But the various aliphatic and aromatic amine derivatives containing substituted 2 - amino benzothiazole attached with chloro acetyl chloride are not completely explored.

Therefore, to enhance the biological activity in the present research work, it is proposed to synthesize some new heterocyclic derivatives that will be better and improved drug with enhanced pharmaceutical and biological properties.

With these new heterocyclic derivatives containing two such nuclei, we have prepared an idea to synthesize some compounds containing (1'-chloro acetyl) substituted 2 - amino benzothiazole nucleus attached with various aliphatic and aromatic amine nuclei to get some new biologically active and useful drugs for human life.

Annexure-IV

Major hypothesis

The literature survey related to benzothiazole and substituted 2 - amino benzothiazole represent that compounds with these nuclei play an important role in the field of pharmaceutical chemistry.

Similarly, chloro acetyl chloride and various aliphatic and aromatic amine derivatives are also known for their biological importance in individual aspects.

Substituted 2 - amino benzothiazole nucleus attached with chloro acetyl chloride will be reacted with various aliphatic and aromatic amine derivatives to form some novel heterocyclic compounds. We expect these newly formed heterocyclic compounds will have enhanced useful biological properties and lower toxic pharmacological applications which will be used not only for human life but also for some industries.

Annexure-V

Research methodology

The following steps will be the research methodology for the proposed research work:-

1) **Synthesis of substituted 2 - amino benzothiazole derivatives**:- It may be prepared either by thiocynogenation of substituted aniline using KSCN (potassium thio cyanate) and bromine in glacial acetic acid or by the reaction of para substituted aniline with NaSCN (sodium thiocyanate) in the presence of H_2SO_4 which act as catalyst.

2) **Synthesis of chloro acetyl chloride**:- It may be prepared either by the carbonylation of methylene chloride or by the addition of chlorine to ketene.

3) **Synthesis of (1'-chloro acetyl) substituted 2 - amino benzothiazole**:- It may be prepared either by the reaction of substituted 2 - amino benzothiazole with chloro acetyl chloride in Et_3N (triethyle amine) or by refluxing equimolar mixture of substituted 2 - amino benzothiazole and chloro acetyl chloride in chloroform in the presence of K_2CO_3.

4) **Synthesis of various aliphatic and aromatic amino acetyl derivatives of substituted 2 -amino benzothiazole**:- It may be prepared either by the reaction of (1'-chloro acetyl) substituted 2 - amino benzothiazole with various amine [aliphatic and aromatic] derivatives in methanol (CH_3OH).

5) **Thin layer chromatography of synthesized compounds** :-It will be proceeded after the purification and recrystallization.

6) **Structure elucidation**:- It will be done with help of spectra.
   a. **I.R spectra**: - It will be recorded and absorption band will be assigned to vibration of different bonds.

   b. **NMR spectra of synthesized compound**:- It will be recorded and chemical shift to various peaks will be determined.

7) **Biological activities**:- Biological study for potential biological activities like antimicrobial, antibacterial anticancer, antifungal, anti-inflammatory etc. will be evaluated by using standard techniques that is filter paper disk technique, radial growth technique for antibacterial and anti fungal respectively, results will be compared with standard drugs.

Bibliography

1. Rana A., Siddiqui N. and Khan S.A.; *Indian J. Pharma. Sci.*, 2007, 69(1), 10-17.
2. Yadav P.S., Devprakash and Senthilkumar G.P.; *International Journal of Pharmaceutical Sciences and Drug Research*, 2011, 3(1), 01-07.
3. Mohamed A. Abdelgawad, Khaled R.A. Abdellatif and Ahmed O.M., Abdegawad et al.; *Medicinal Chemistry*, 2014, S1.
4. Gilani S. J., Khan S. A., Siddiqui N.,Verma S. P., Mullick P. and Alam A.; *Medicinal Chemistry*, 2011, 26(3), 332-340.
5. Maru J., Patel G.R., Yadav R. and Bhatt B; *J. Curr. Chem. Pharm. Sc.*, 2014, 4(4), 164-171.
6. Hadanu R., Idris S. and Sutapa I.W.; *Indones. J. Chem.*, 2015, 15(1), 86-92.
7. Asif S., Navin B.P. and Rajani D.; *Indian Journal of Research in Pharmacy and Biotechnology*, 2014, 936-942.
8. Jena J.; *International Journal of Pharmacy and pharmaceutical sciences*, 2014, 6(2), 16-22.
9. Yadav A.G., Patil V.N., Asrondkar A.L., Naik A.A., Anshulkar P.V., Bobade A.S. and Choudhary A.S.; *RASAYAN J. Chem.*, 2012, 5(1), 117-120.
10. Suresh C., Rao V., Jayaveera K.N. and Reddy G. J.; *International J. Pharmacy & Bio. Sciences*: 2011, 1(4), 409-411.
11. Khokra S. L., Arora K., Mehta H., Aggarwal A. and Yadav M.; *International Journal of Pharmaceutical Sciences and Research*, 2011, 2(6), 1356-1377.
12. Imamura H. A., Noriyuki T.D., Nishimura N., Masami O. and Yohino K.; *Chem. Abstract*, 1990, 112, 25684.
13. Kumar A.V., Alex M. and Kumar A.; *International Journal of Pharmaceutical Research & Development*, 2014, 6(8), 80-85.
14. Rajeeva B., Srinivasulu N. and Shantaumar S. M.; *E- Journal of Chemistry*, 2009, 6(3),775-779.
15. Sankar R., Reddy D. and Sudhakar D.; *Scholars Research Library, Der Pharma Chemica.*, 2014, 6(1), 111-114.
16. Shafi S., Alam M. M. and Mulakayala N. et al.; *European Journal of Medicinal Chemistry*, 2012, 49, 324-333.
17. Shanmukha I., Madhusudan M., Jayachandra E., Vijay K. M. and Prakash B.; *British Journal of Pharmaceutical Research*, 2014, 4(6), 759-769.
18. Siddiqui N. and Ruhi A.; *World Journal of Pharmacy and Pharmaceutical Science*, 2014, 3(3), 1450-1458.

19. Kaur H., Kumar S., Singh I., Saxena K. K. and Kumar A.; *Digest Journal of Nanomaterial and Biostructures*, **2010**, 5(1), 67-76.
20. Mehtab R., Srivastava A., Gupta N., Kushwaha S. K. and Tripathi A.; *Journal of Chemical and Pharmaceutical Sciences*, **2014**, 7(1), 34-38.
21. Petal R. V., Petal P.K., Kumari P., Rajani D. P. and Chikhalia K. H.; *European Journal Medicinal Chem.*, **2012**, 53, 41-51.
22. Verma S. M., Dadheech M. and Meena R. P.; *Journal of Pharma. Sci. Tech.*, **2012**, 1(2), 30-35.
23. Algul O., Kaessler A., Apcin Y., and Yilmaz A. Z.; *Molecules*, **2008**, 13736.
24. Paramashivappa R., Phani P. K. and Rao A. S.; *Bioorganic Medicinal Chemistry Lett.*, **2003**, 3(4), 657.
25. Mahran M. A., Elnassry S. M., Allam S. R. and EL- Zawaway L. A.; *Pharmazie*, **2003**, 58(8), 527.
26. Pareek A., Pareek D., Choudhary M. and Ojha K..G.; *Scholars Research Library, Der Pharma Chemica*, **2010**, 2(5), 281.
27. Ailio S., Well G., Stone E., Kadri H. and Bell R.; *Journal of Medicinal Chemistry*, **2008**, 51, 5035.
28. Delmas F., Avellaneda A. and Giorgio C. D. et al; *European Journal of Medicinal Chemistry*, **2004**, 39(8), 685-690.
29. Yar M. S. and Ansari Z.H.; *Acta Polonial Pharmaceutical Drug Research*, **2009**, 66, 387-392.
30. Choudhary M., Pareek D., Pareek P. K., Kant R., Ozha K. G. and Pareek A.; *Bull Korean Chem. Soc.*, **2011**, 32(1), 131-136.
31. Wu C., Wei J., Gao K. and Wang Y.; *Bioorganic and Medicinal Chemistry*, **2007**, 15, 2789-2796.
32. Diouf O., Depreux P., Lesieur D., Poupaert J. H. and Caignard D. H; *European Journal of Medicinal Chemistry*, **1995**, 30, 715-719.
33. Sparks R. B., Polam P., Zhu W., Crawley M. L., Takvorian A., Mclaughlin E., Wei M., Ala P. J., Gonneville L., Taylor N., Li Y., Wynn R., Burn T. C., Liu PCC. and Combs A. P.; *Bioorganic and Medicinal Chemistry Letters*, **2007**, 17, 736-740.
34. Gurupadayya, B. M., Manohara, Y. N. and Gopal; *M. Indian J. Heterocycle Chem.*, **2005**, 15, 113.
35. Kumbhare R. M., Dalmal T., Kosurkar U., Sridhar V. and Rao J. V.; *Bioorganic & Medicinal Chemistry Letters*, **2012**, 22, 453-455.
36. Hassan G. S., Awdallah F. M., Saadi M. T. El., Elgaendi A. O. and Hemeda L.R.; *Journal of Chemical & Pharmaceutical Research*, **2015**, 7(7), 1125-1143.
37. Malik J. K., Dr. Manvi F. V., Dr. Nanjwade B. K. and Purohit P.; *Journal of Pharmacy Research*, **2009**, 2(11), 1687-1690.
38. Choudhary M., Pareek D., Anuja, Ojha K. G. and Pareek A.; *International Journal of Current Chemistry*, **2010**, 1(3), 179-183.
39. Doma A., Kulkarni R., Garlapati A. and Krishna P. R.; *Pharmacophore*, **2014**, 5(2), 331-342.

40. Patel P., Pillai J., Darji N. and Patel B.; *Int. J. Drug Res. Tech.*, 2012, 2(2), 170-176.
41. Saarangi R., Suvendu S. and Sudhakar B.; *Sch. Acad. J. Pharm.* 2013, 2(3), 233-240.
42. Deshpande V. G, Habib S. I., Azam N. and. Kulkarni P. A: *International Journal of Applied Biology and Pharmaceutical Technology*, 2015, 6(2), 261-266.
43. Chandramouli, Shivanand M.R., Nayanbhai T. B., Bheemachari and Udupi R. H.; *Journal of Chemical & Pharmaceutical Research*, 2012, 4(2), 1151-1159.
44. Verma A. K, Martin A. and Singh A. K. (Sr.); *International J. Pharm. Biol. Res.*, 2014, 2(3), 84-89.
45. Munirajasekhar D., Himaja M. and Mali S.V.: *International Research Journal of Pharmacy*, 2011, 2(1), 114-117.
46. Caracci A., Defrenza I., Muraglia M., Carrieri A., Bambeke F. V., Rosato A., Corbo F. and Franchini C.: *European Journal of Medicinal Chemistry*, 2013, 64, 357-364.
47. Patel N. S., Beranek P., Nebyla M., Pribyl M. and Snita D.: *Int. J. Electrochem. Sci*, 2014, 9, 3951-3960.
48. Udhayakala P. and Rajendiran T. V.: Scholars Research Library, *Der Pharma Chemica*, 2015, 7(1), 92-99.
49. Mahajan D. P., Bhosale J. D. and Bendre R. S.: *Journal of Applicable Chemistry*, 2013, 2(4), 765-771.
50. Lacova M., Chovancova J., Hyblova O. and Varkonda S.; *Chem. Papers*, 1991, 45(3), 411-418.
51. Singh S., Kumar V., Sharma S. K., Kumar A. and Sharma S.: *Oriental Journal of Chemistry*, 2010, 26(1), 93-101.
52. Rajasekarnan A., Periasany M. and Venkatesan S.: *Journal of Development Biology & Tissue Engineering*, 2010, 2(1), 5-13.
53. Srivastava S.D. and Sen J. P.; *Indian Journal of Chemistry*, 2008, 47B, 1583-1586.
54. Suresh C., Rao J. V., Jayaveera K. N. and G. Jayapal Reddy: *International Journal of Pharmacy & Biological Sciences*, 2011, 1(4), 409-413.
55. Joshap J. and Boomadevi J.: *Journal Mater. Environ. Science*, 2014, 5(3), 693.
56. Kumar A., Kumar P., Kumar U. and Kumar R.; *Reserch Journal of Pharmaceutical, Biological and Chemical Sciences*, 2012, 3(4), 847.
57. Bhoi M. N., Borad M. A., Panchal N. K. and Patel H. D.: *International Letters of Chemistry, Physics and Astronomy*, 2015, 53, 106-113.
58. Chavan A. A. and Pai N. R.: *Molecules*, 2007, 12, 2467-2477.
59. Kaur H., Kaur H., Chawla A., Baghel U. S. and Dhawan R. K.: *Journal of Global Trends in Pharmaceutical Sciences*, 2014, 5(2), 1684-1691.
60. Mariappan G., Prabhat P., Sutharson T., Banerjee J. and Pantangia U., *Journal of the Korean Chemical Society*, 2012, 56(2), 251.

61. Bhausaheb D. K., Madhukar G. V. and Balkrishna S. S.: *International Journal of Pharmacy & Pharmaceutical Research*, 2015, 3(1), 112-124.

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